

### **DETAILED ACTION**

The Amendment received on 03/21/2008, wherein claims 1, 3, 9 have been amended, and claims 5-7 have been canceled. Applicant's amendment also added new claim 28.

Applicant's cancellation of claims 5-7 overcomes the rejection of claims 5-7 under 35 U.S.C. 112, first paragraph, for scope of enablement.

Applicant's amendment by deleting the recitation "derivative" overcomes the rejection of claims 1-8 under 35 U.S.C. 112, second paragraph, as being indefinite.

Applicant's arguments have been considered, but not found persuasive, the rejection of claims 1-2, 4, 8-9 under 35 U.S.C. § 103(a) as being unpatentable over Powis et al. (Anti-Cancer Drugs 1996, 7 (suppl 3), pages 121-126, PTO-1449), and in view of Halperin et al. (US 5,633,274, PTO-1449) is MAINTAINED. See under response to arguments.

Applicant's arguments have been considered, but not found persuasive, the rejection of claims 1-2, and 8-9 under 35 U.S.C. § 103(a) as being unpatentable over Oblong et al. (Cancer Chemother. Pharmacol. 1994, 34: 434-438, PTO-1449), and in view of Halperin et al. (US 5,633,274, PTO-1449) is MAINTAINED. See under response to arguments.

Applicant's arguments have been considered, but not found persuasive, the rejection of claims 1-2, 4, and 9 under 35 U.S.C. § 103(a) as being unpatentable over Kirkpatrick et al. (Eur. J. Med. Chem 1992, 27, pages 33-37; PTO-1449), in view of

Halperin et al. (US 5,633,274, PTO-1449) is MAINTAINED. See under response to arguments.

Applicant's arguments have been considered, but not found persuasive, the rejection of claim 3 under 35 U.S.C. § 103(a) as being unpatentable over Powis et al. (Anti-Cancer Drugs 1996, 7 (suppl 3), pages 121-126, PTO-1449) or Oblong et al. (Cancer Chemother. Pharmacol. 1994, 34: 434-438, PTO-1449), and in view of Royer (US 5,783,214, PTO-892) is MAINTAINED. See under response to arguments.

Claims 1-4, 8-9, and 28 are examined herein.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-2, 4, 8-9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Powis et al. (Anti-Cancer Drugs 1996, 7 (suppl 3), pages 121-126, PTO-1449), and in view of Halperin et al. (US 5,633,274, PTO-1449).

Powis et al. disclose compounds such as 1-methylpropyl 2-imidazolyl disulfide, and benzyl 2-imidazolyl disulfide in a pharmaceutically acceptable carrier, for the use of thioredoxin reductase inhibition. See compounds IV-2 and DLK-36, page 124 of Powis. Powis et al. teaches a composition comprising 1-methylpropyl 2-imidazolyl disulfide. It is

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also taught that the alkyl 2-imidazolyl compounds, 1-methylpropyl 2-imidazolyl disulfide exhibits dose-dependent antitumor activity against human MCF-7 breast cancer xenografts growing. See page 124.

Powis et al. does not teach the employment of a polymer in the composition comprising asymmetric disulfide.

Powis et al. do not teach employment of another chemotherapeutic in the composition therein.

Halperin et al. teaches that active agents that inhibit cancer cell proliferation can be administered in a variety of formulations including sustained release delivery systems containing polymer matrix. It is also taught that the sustained release delivery systems include erosional systems in which the active agent is contained in a form within a matrix. See column 6, lines 1-30. It is also taught that the agents therein which inhibit cancer cell proliferation can be delivered in the form of anti-cancer cocktails with other anti-cancer agents or chemotherapeutic agent. See column 6, line 64-column 7, line 25.

It would have been obvious to a person of ordinary skill in the art at the time of invention to employ 1-methylpropyl 2-imidazolyl disulfide in a polymer matrix because Halperin teaches that compounds that inhibit cancer cell proliferation can be administered in a variety of formulations which include entrapping in a polymer. One of ordinary skill in the art at the time of invention would have been motivated to employ asymmetric disulfide in a matrix comprising a polymer with the expectation of obtaining

a sustained release delivery system that has the capability of releasing the active ingredient i.e asymmetric disulfide in a controlled rate.

It would have been obvious to a person of ordinary skill in the art to employ a chemotherapeutic agent in the composition comprising asymmetric disulfide. It is generally considered *prima facie* obvious to combine compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. As shown by recited teachings of Powis et al. and Halperin et al. the instant claims contain two compositions used for treatment of cancer i.e an asymmetric disulfide, and a chemotherapeutic agent. *In re Kerkhoven*, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980).

Furthermore, as the combined teachings of Powis et al., and Halperin et al. renders the claimed composition obvious, the property of such a claimed composition will also be rendered obvious by the prior art teachings, since the properties, namely “wherein said composition erodes and releases the asymmetric disulfide”, in claim 2, are inseparable from its composition. Therefore, if the prior art teaches the composition or renders the composition obvious, then the properties are also taught or rendered obvious by the prior art. *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

### ***Response to Arguments***

Applicant argues that "The Office has provided no evidence that one ordinarily skilled in the art would recognize that the sustained release delivery systems disclosed in Halperin for imidazoles would be suitable for asymmetric disulfides disclosed in Powis. There is no structural relationship between the imidazoles of Halperin and the asymmetric disulfides of the present claims." These arguments have been considered, but not found persuasive. Powis teaches that the alkyl 2-imidazolyl compounds, 1-methylpropyl 2-imidazolyl disulfide exhibits antitumor activity against human MCF-7 breast cancer xenografts growing. Halperin et al. broadly teaches that active agents that inhibit cancer cell proliferation can be administered in a variety of formulations including sustained release delivery systems containing polymer matrix. Thus even though Halperin et al. does not exemplify asymmetric disulfides, it has been well-established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in light of the admitted knowledge in the art, to person of ordinary skill in the art. In re Boe, 355 F.2d 961, 148 USPQ 507, 510 (CCPA 1966); In re Lamberti, 545 F.2d 747, 750, 192 USPQ 279, 280 (CCPA 1976); In re Fracalossi, 681 F.2d 792, 794, 215 USPQ, 570 (CCPA 1982); In re Kaslow, 707 F.2d 1366, 1374, 217 USPQ 1089, 1095 (Fed. Cir. 1983). One of ordinary skill in the art at the time of invention would have been motivated to employ anticancer agent, asymmetric disulfide in a matrix comprising a polymer with the expectation of obtaining a sustained release delivery system that has the capability of releasing the active ingredient i.e asymmetric disulfide in a controlled rate because

Halperin teaches that compounds that inhibit cancer cell proliferation can be administered in a variety of formulations which include entrapping in a polymer for sustained release delivery.

Applicant argues that “Additionally, as expressly set forth in the specification, the sustained delivery of asymmetric disulfides resulted in an unexpectedly increased and prolonged decrease in thioredoxin levels. Specifically, Applicant has provided evidence comparing the level and length of inhibition of thioredoxin levels following (i) a 1 hour infusion of 1-methylpropyl 2-imidazolyl disulfide (also referred to as PX-12) and (ii) a sustained 3 hour infusion of 1-methylpropyl 2- imidazolyl disulfide. As shown in Figure 3, when the infusion length was increased to 3 hours (from 1 hour as shown in Figure 2), the thioredoxin levels were constantly decreased at significantly lower levels and these decreased thioredoxin levels were consistently maintained for a significantly longer period of time. Such greater than expected results are evidence of the nonobviousness of the present claims. See MPEP 716.02(a).” Applicant's arguments with respect to unexpected results herein have been fully considered but are not deemed persuasive as to the nonobviousness and/or unexpected results of the claimed invention over the prior art, since the results are not commensurate with the instant claims. Instant claims are drawn to a composition comprising an asymmetric disulfide, and a matrix which contains a polymer. The results provide no clear and convincing evidence of nonobviousness or unexpected results over the cited prior art because results merely demonstrate the decrease of thioredoxin employing the sustained 3 hour infusion of one particular asymmetric disulfide, 1-methylpropyl 2- imidazolyl disulfide,

and is not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the compounds i.e any asymmetric disulfide in combination with a polymer in the claimed composition. See MPEP 716.02. Therefore, the evidence presented in specification herein is not seen to be clear and convincing in support of the nonobviousness of the instant claimed invention over prior art.

Claims 1-2, 4, and 8-9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Oblong et al. (Cancer Chemother. Pharmacol. 1994, 34: 434-438, PTO-1449), in view of Halperin et al. (US 5,633,274, PTO-1449).

Oblong et al. disclose compositions comprising asymmetric imidazolyl disulfides such as 1-methylpropyl 2-imidazolyl disulfide of the instant invention for the inhibition of cellular proliferation involving thioredoxin, thioredoxin reductase in an aqueous solution which is a pharmaceutical carrier. See compounds IV-2 Fig. 1. Page 435. Employment of this compound in 0.2 M phosphate buffer is also disclosed. See page 435, right column, bottom paragraph, lines 4-6.

Oblong et al. does not teach the employment of a polymer in the composition comprising asymmetric disulfide.

Oblong et al. do not teach employment of another chemotherapeutic.

Halperin et al. teaches that active agents that inhibit cancer cell proliferation can be administered in a variety of formulations including sustained release delivery systems containing polymer matrix. It is also taught that the sustained release delivery systems include erosional systems in which the active agent is contained in a form

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within a matrix. See column 6, lines 1-30. It is also taught that the agents therein which inhibit cancer cell proliferation can be delivered in the form of anti-cancer cocktails with other anti-cancer agents or chemotherapeutic agent. See column 6, line 64-column 7, line 25.

It would have been obvious to a person of ordinary skill in the art at the time of invention to employ 1-methylpropyl 2-imidazolyl disulfide, an agent that inhibits cell proliferation according to Oblong et al. in a polymer matrix because Halperin teaches that compounds that inhibit cancer cell proliferation can be administered in a variety of formulations which include entrapping in a polymer. One of ordinary skill in the art at the time of invention would have been motivated to employ asymmetric disulfide in a matrix comprising a polymer with the expectation of obtaining a sustained release delivery system that has the capability of releasing the active ingredient i.e asymmetric disulfide in a controlled rate.

It would have been obvious to a person of ordinary skill in the art to employ a chemotherapeutic agent in the composition comprising asymmetric disulfide. It is generally considered *prima facie* obvious to combine compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. As shown by recited teachings of Oblong et al. and Halperin et al. the instant claims contain two compositions used for treatment of cancer i.e an asymmetric disulfide, and a chemotherapeutic agent. *In re Kerkhoven*, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980).

Furthermore, as the combined teachings of Oblong et al., and Halperin et al. renders the claimed composition obvious, the property of such a claimed composition will also be rendered obvious by the prior art teachings, since the properties, namely “wherein said composition erodes and releases the asymmetric disulfide”, in claim 2, are inseparable from its composition. Therefore, if the prior art teaches the composition or renders the composition obvious, then the properties are also taught or rendered obvious by the prior art. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

### ***Response to Arguments***

Applicant's arguments have been considered, but not found persuasive for reasons as set forth above (See under Response to Arguments, for Powis et al. rejection).

Claims 3, and 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Powis et al. (Anti-Cancer Drugs 1996, 7 (suppl 3), pages 121-126, PTO-1449) or Oblong et al. (Cancer Chemother. Pharmacol. 1994, 34: 434-438, PTO-1449), and in view of Royer (US 5,783,214, PTO-892).

Powis et al., and Oblong et al. are applied as discussed in the above rejection.

Powis et al. or Oblong et al. do not teach the employment of a hydrophilic polymer in the composition comprising asymmetric disulfide.

Royer teaches sustained release delivery system comprising a gel matrix comprising hydrophilic polymer, gelatin for drugs which include anticancer drugs. It is taught that the delivery system therein provides easy control of release profile for drugs. See column 9, lines 16-20.

It would have been obvious to a person of ordinary skill in the art at the time of invention to employ 1-methylpropyl 2-imidazolyl disulfide, an agent that inhibits cell proliferation according to Powis et al. or Oblong et al. in a hydrophilic polymer matrix, gelatin because Royer teaches that anticancer drugs are incorporated into gel matrix which contains gelatin. One of ordinary skill in the art at the time of invention would have been motivated to employ asymmetric disulfide in a gel matrix comprising a hydrophilic polymer, gelatin with the expectation of obtaining a sustained release delivery system that has the capability of releasing the asymmetric disulfide in a controlled rate.

### ***Response to Arguments***

Applicant argues that “as noted by Royer, delivery systems of medicinal agents is a challenge because, among other things, the medicinal may be chemically modified during formulation. The delivery systems of Royer are specifically designed for the delivery of proteins, and there is no teaching or suggestion that the delivery of proteins using the systems of Royer could be applied to asymmetric disulfides”. Applicant’s arguments have been considered, but not found persuasive. Powis teaches that the alkyl 2-imidazolyl compounds, 1-methylpropyl 2-imidazolyl disulfide exhibits antitumor activity against human MCF-7 breast cancer xenografts growing. Royer teaches

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sustained release delivery system comprising a gel matrix comprising hydrophilic polymer, gelatin for drugs which include anticancer drugs. Thus even though Royer does not exemplify asymmetric disulfides as anticancer drugs employed therein, it has been well-established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in light of the admitted knowledge in the art, to person of ordinary skill in the art. In re Boe, 355 F.2d 961, 148 USPQ 507, 510 (CCPA 1966); In re Lamberti, 545 F.2d 747, 750, 192 USPQ 279, 280 (CCPA 1976); In re Fracalossi, 681 F.2d 792, 794, 215 USPQ, 570 (CCPA 1982); In re Kaslow, 707 F.2d 1366, 1374, 217 USPQ 1089, 1095 (Fed. Cir. 1983). One of ordinary skill in the art at the time of invention would have been motivated to employ asymmetric disulfide in a gel matrix comprising a hydrophilic polymer, gelatin with the expectation of obtaining a sustained release delivery system that has the capability of releasing the anticancer agent, asymmetric disulfide in a controlled rate, since Royer broadly teaches that anticancer drugs are incorporated into gel matrix which contains gelatin for easy control of release profile for drugs .

Claims 1-2, 4, and 9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kirkpatrick et al. (Eur. J. Med. Chem 1992, 27, pages 33-37; PTO-1449), in view of Halperin et al. (US 5,633,274, PTO-1449).

Kirkpatrick et al. disclose compounds 1-methylpropyl 2-imidazolyl disulfide (IV-2) of the instant invention for the evaluation of selective cytotoxicity to hypoxic EMT6 tumor

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cells. See compounds 11, Table II. Page 34; page 35, right column, lines 1-3. Employment of this compound in 75 mL of 0.05 potassium phosphate buffer containing 0.1 M KCl is also disclosed. See page 37, left column, 2<sup>nd</sup> para from bottom.

Kirkpatrick et al. does not teach the employment of a polymer in the composition comprising disulfide.

Halperin et al. teaches that active agents that inhibit cancer cell proliferation can be administered in a variety of formulations including sustained release delivery systems containing polymer matrix. It is also taught that the sustained release delivery systems include erosional systems in which the active agent is contained in a form within a matrix. See column 6, lines 1-30. It is also taught that the agents therein which inhibit cancer cell proliferation can be delivered in the form of anti-cancer cocktails with other anti-cancer agents or chemotherapeutic agent. See column 6, line 64-column 7, line 25.

It would have been obvious to a person of ordinary skill in the art at the time of invention to employ 1-methylpropyl 2-imidazolyl disulfide in a polymer matrix because Halperin teaches that compounds that inhibit cancer cell proliferation can be administered in a variety of formulations which include entrapping in a polymer. One of ordinary skill in the art at the time of invention would have been motivated to employ asymmetric disulfide in a matrix comprising a polymer with the expectation of obtaining a sustained release delivery system that has the capability of releasing the active ingredient i.e asymmetric disulfide in a controlled rate.

Furthermore, as the combined teachings of Kirkpatrick et al., and Halperin et al. renders the claimed composition obvious, the property of such a claimed composition will also be rendered obvious by the prior art teachings, since the properties, namely “wherein said composition erodes and releases the asymmetric disulfide”, in claim 2, are inseparable from its composition. Therefore, if the prior art teaches the composition or renders the composition obvious, then the properties are also taught or rendered obvious by the prior art. *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

### ***Response to Arguments***

Applicant’s arguments have been considered, but not found persuasive for reasons as set forth above (See under Response to Arguments, for Powis et al. rejection).

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

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F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 8-9, and 28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 49, 52-60, 63-69, and 71 of copending Application No.10/366,751. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of '751 are drawn to a composition comprised of a pharmacologically effective amount of a salt of 1-methylpropyl 2-imidazolyl disulfide and a pharmaceutically acceptable carrier, and instant claims are drawn to the composition comprising 1-methylpropyl 2-imidazolyl disulfide or a derivative thereof, and a matrix including a polymer.

It would be obvious to one of ordinary skill in the art to employ salt of 1-methylpropyl 2-imidazolyl disulfide as the derivative of 1-methylpropyl 2-imidazolyl disulfide. One of ordinary skill in the art would have been motivated to employ salt of 1-methylpropyl 2-imidazolyl disulfide with reasonable expectation of obtaining a composition effective as an inhibitor of cellular redox signaling. Further, a derivative of 1-methylpropyl 2-imidazolyl disulfide can include salts, and thus the instant claims and the composition claimed in the copending application '751 are substantially overlapping.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-4, 8-9, and 28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-10 of copending Application No.10/600957. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of '957 are drawn to a composition comprising 2-imidazolyl disulfide and a pharmaceutically acceptable carrier, and instant claims are drawn to a composition comprising asymmetric disulfide or a derivative thereof, and a matrix including a polymer.

It would be obvious to one of ordinary skill in the art to employ 2-imidazolyl disulfide as asymmetric disulfide or derivative thereof. One of ordinary skill in the art would have been motivated to employ 2-imidazolyl disulfide with reasonable expectation of obtaining a composition effective as an inhibitor of cellular redox signaling. Further, the species composition comprising a 2-imidazolyl disulfide that is useful in reducing or eliminating thioredoxin associated apoptosis inhibition claimed in the conflicting '957 application appears to fall within the same scope of the genus composition comprising an asymmetric disulfide or derivative thereof, wherein said asymmetric disulfide is an inhibition of thioredoxin or thioredoxin reductase claimed in the application being examined.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Response to Arguments***

Applicant's arguments have been considered, but not found persuasive for reasons as set forth above.

### ***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period, will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Thursday, 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax

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phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shobha Kantamneni, Ph.D

Patent Examiner

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/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617